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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	04995.0032-0	7721

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EXAMINER
ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
1645	29

DATE MAILED: 09/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/215,163	Applicant(s) STINSON ET AL.
	Examiner Robert A. Zeman	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14,17-20,23,29 and 32-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14,17-20,23,29 and 32-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 2-19-2003 are acknowledged. Claims 1 and 32-40 have been amended. Claims 13 and 15-16 have been canceled. Claims 1, 2, 14, 17-20, 23, 29 and 32-43 are pending and currently under examination.

The declaration of Hing C. Wong under 37 C.F.R. 1.132 is acknowledged and has been fully considered.

Claim Objections Withdrawn

The objection to claim 32 for containing an obvious typographical error is withdrawn in light of the amendment thereto.

The objection to claim 34 for starting with an improper article is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 13 and 17 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "Shiga toxin type 2 variants" is withdrawn. Cancellation of claim 13 has rendered the rejection moot.

The rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "is from the sequence set forth in SEQ ID NO:42 and SEQ ID NO:44" is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claim 32 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "comprises amino acid sequences" is withdrawn.

Applicant's argument has been fully considered and deemed persuasive. Based on Applicant's statements, the antibodies the instant claims contain **all** the recited in the Markush group in addition to other sequences (i.e. framework sequences).

Claim Rejections Maintained

Double Patenting

The rejection of claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 is maintained for reasons of record. Applicant has indicated that they will be submitting a Terminal Disclaimer under separate cover.

Claims 1-2, 14, 17-20, 23, 29 and 32-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679) is maintained for reasons set forth in the rejection of claims 1-2, 13-20, 23, 29 and 32-41 in the previous Office action. Applicant has indicated that they will be submitting a Terminal Disclaimer under separate cover.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 14, 17-20, 29, 32-40 and 43-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized monoclonal antibodies

based on monoclonal antibodies 13C4 or 11E10 (**defined regions**), does not reasonably provide enablement for humanized antibodies "containing at least part of a murine immunoglobulin variable region as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 mainly for the reasons set forth in the previous Office action in the rejection of claims 1, 2, 13-20, 23, 29 and 32-41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Applicant argues that the instant claims are all based on the 13C4 or 11E10 monoclonal antibodies. It should be noted that the specification is enabled for the humanized 13C4 and 11E10 monoclonal antibodies as recited in claim 41. However, the instant claims merely require that the murine immunoglobulin variable region have **one amino acid** in common with the variable regions depicted in Figures 3 or Figure 6 or SEQ ID NO:42 or SEQ ID NO:44 (i.e. "at least part of..."). As outlined previously, the specification outlines the materials and methods needed to make humanized antibodies utilizing the 13C4 or 11E10 monoclonal antibodies. However, the specification is silent on the sequences of the murine variable region required to confer function on the chimeric antibody the location (or sequence) of the immunogenic epitopes. Given the lack of guidance contained in the specification and the unpredictability in determining acceptable sequence variations, one of skill in the art could not make the broadly claimed invention without undue experimentation.

Claims 23, 29 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10 (**defined sequences**), does not reasonably provide enablement for pharmaceutical compositions comprising humanized antibodies "containing at least part of a murine immunoglobulin variable region as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 mainly for the reasons set forth in the previous Office action in the rejection of claims 23 and 29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Contrary to Applicant's assertion, the amendment to claim 1 is not sufficient to obviate the aforementioned rejection. As outlined previously, the specification is silent on how the claimed compositions would be used and equally silent on the efficacy of a given composition. Since no evidence has been provided that illustrates or even suggests that the claimed pharmaceutical compositions are capable of eliciting a beneficial therapeutic response, one of skill in the art would not be able to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of term "variable region contains at least part of the CDR sequences located as follows...", is maintained.

Applicant argues that said rejection was addressed by amendment. The aforementioned claim, contrary to Applicant's assertion, has not been amended and hence the rejection is maintained.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 14, 17-20, 23, 29 and 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Carter et al. (WO 94/04679) for the reasons set forth in the previous Office action in the rejection of claims 1, 2, 13-20, 23, 29 and 32-41.

Applicant argues:

1. The chimeric antibody disclosed by Carter et al. contains a mouse-human variable region whereas the antibodies of the instant invention (claim 1) feature a murine variable region.

2. It is not obvious from the combination of the cited references how to obtain the amino acid sequence for the 13C4 or 11E10 murine antibodies.

3. Dr. Wong in his Declaration states that it would not be obvious to identify the sequence of 13C4 and 11E10 using the approach suggested by the USPTO at page 9 of the Office action.

4. Dr. Wong confirms that none of the references by Spiers, O'Brien, Carter and Shitara disclose nucleic acid or amino acid sequence information that would be useful to clone the 13C4 or 11E10 murine antibodies.

5. Dr. Wong states that the approach suggested by the examiner would not work and hence one of skill in the art would be dissuaded from isolating the sequence of the 13C4 and 11E10 murine antibodies.

6. Dr. Wong states that due to the genetic complexity of the 13C4 and 11E10 murine antibody variable regions would make using the Examiner's approach to isolate cDNA from a hybridoma library very difficult with no reasonable chance of success.

7. The approach taken by the inventors took into account the problems inherent to the approach proposed by the Examiner.

8. The PCR amplification problem (and its solution) is not disclosed by any of the cited references.

Applicant's arguments and the Declaration by Dr. Wong have been fully considered and deemed non-persuasive. As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies and that Carter et al. disclose the methods of producing humanized antibodies. Furthermore, though the sequences of said antibodies ~~where~~ were not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods. Moreover, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Carter et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. It should be noted that Dr. Wong's arguments are predicated on the mistaken belief that the Examiner implied that the cloning approach described by Carter could be used to obtain the sequences of the 11E10 and 13C4 antibodies. As reiterated above, said sequences could be obtained by standard sequences methodologies. Finally, since the rejected claims are not product by process claims, the products disclosed by the cited references, in absence of evidence to the contrary, are deemed to be the same as those of the instant invention.

Claims 1, 2, 14, 17-20, 23, 29 and 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692) for the reasons set forth in the previous Office action in the rejection of claims 1, 2, 13-20, 23, 29 and 32-41.

Applicant argues:

1. The chimeric antibody disclosed by Carter et al. contains a mouse-human variable region whereas the antibodies of the instant invention (claim 1) feature a murine variable region.

2. It is not obvious from the combination of the cited references how to obtain the amino acid sequence for the 13C4 or 11E10 murine antibodies.

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5. Dr. Wong states that the approach suggested by the examiner would not work and hence one of skill in the art would be dissuaded from isolating the sequence of the 13C4 and 11E10 murine antibodies.

6. Dr. Wong states that due to the genetic complexity of the 13C4 and 11E10 murine antibody variable regions would make using the Examiner's approach to isolate cDNA from a hybridoma library very difficult with no reasonable chance of success.

7. The approach taken by the inventors took into account the problems inherent to the approach proposed by the Examiner.

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Applicant's arguments and the Declaration by Dr. Wong have been fully considered and deemed non-persuasive. As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies and that Carter et al. disclose the methods of producing humanized antibodies. Furthermore, though the sequences of said antibodies where not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods. Moreover, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Carter et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. It should be noted that Dr. Wong's arguments are predicated on the mistaken belief that the Examiner implied that the cloning approach described by Shitara could be used to obtain the sequences of the 11E10 and 13C4 antibodies. As reiterated above, said sequences could be obtained by standard sequences methodologies. Finally, since the rejected claims are not product by process claims, the products disclosed by the cited references, in absence of evidence to the contrary, are deemed to be the same as those of the instant invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Robert A. Zeman
September 15, 2003